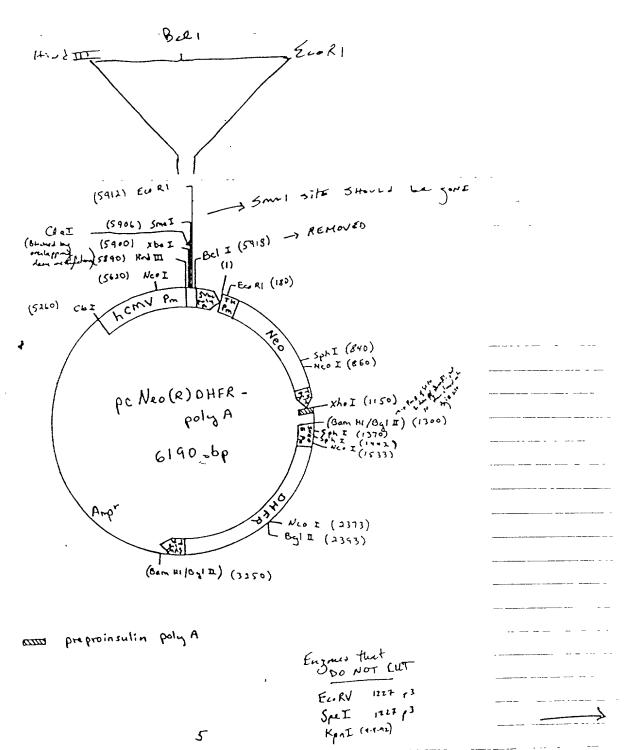
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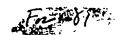
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Gary S. Gray, Jerry Carson, Kashi Javaherian, Paul D. Rennert and Sandra Silver

Serial No.: 09/227,595 09/227,5

Filed: January 8, 1999 Seanler 20, 2001

For: CTLA4-Cy4 Fusion Proteins (as amended)

Attorney Docket No.: RPN-001

Group Art Unit: 1642

Examiner: Helms, L.

Assistant Commissioner for Patents Washington, D.C. 20231

Certificate of First Class Mailing (37 CFR 1-8(a))

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents,

Washington, D.C. 20231 on the date set forth below.

ber 20, 2001 Date of Signature and of Mail Deposit Bv:

Registration No. Attorney for Applicants

Label No. EL 833315914US

DECLARATION UNDER 37 C.F.R. 1.131 BY

GARY S. GRAY, JERRY CARSON, KASHI JAVAHERIAN, PAUL D. RENNERT AND SANDRA SILVER

Sir:

We, Gary S. Gray, Jerry Carson, Kashi Javaherian, Paul D. Rennert And Sandra Silver declare:

We are the inventors of the subject matter described and claimed in the 1. above-referenced patent application.

2. Prior to July 11, 1994, the invention described and claimed in the above-referenced application was completed in this country, as evidenced by the following:

A. Prior to July 11, 1994, we were in possession of a cloned CTLA4Ig molecule which was producing large amounts of active protein in CHO DG44 cells.

Page A-1 of Appendix A describes amino acid modifications to the Ig portion of the CTLA4Ig molecule. Deletion of the CH₂ domain from γ 1 and mutations to amino acids 235 and 237 in γ 4 are described.

Page A-2 of Appendix A describes amplification of the mutated $\gamma 4$ Hinge-CH₂-CH₃ region and the cloning of the mutated $\gamma 4$ into pNRDSH/hCTLA4 to replace the existing $\gamma 1$ Hinge-CH₂-CH₃.

Page A-3 of Appendix A describes a second method which involves the use of nested PCR to generate a mutated $\gamma 1$ (having an L to A substitution at amino acid 234, an L to E substitution at amino acid 235, and a G to A change at amino acid 237) from hCTLA4Ig and the cloning of the mutated $\gamma 1$ back into hCTLA4 pNRDSH.

Pages A-5 and A-6 show primers for use in making mutated forms of CTLA4Ig.

The notebook pages submitted as pages A-1 through A-7 of Appendix A demonstrate that we completed the claimed invention in this country prior to July 11, 1994.

B. In addition, as shown on page A-8 of Appendix A, prior to July 11, 1994, we demonstrated that mutated forms of CTLA4Ig effectively competed with biotinylated CTLA4-Ig for binding to B7.

In the experiment presented at the bottom of the page B7Ig was put onto plate.

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Date:		Signed:	
Date: ˌ	<u> Jethu 42001</u>	Signed:	Gary S. Gray Jerry Carson
Date:		Signed:	Kashi Javaherian
Date:		Signed:	Paul D. Rennert
Date:		Signed:	Sandra Silver

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Gary S. Gray, Jerry Carson, Kashi Javaherian, Paul D. Rennert and Sandra Silver

Continuation of

Serial No.: 09/227,595

Filed: January 8, 1999 - De Carber 20, 2001

For: CTLA4-Cy4 Fusion Proteins (as amended)

Attorney Docket No.: RPN-001

Group Art Unit: 1642

Examiner: Helms, L.

1.10

Assistant Commissioner for Patents Washington, D.C. 20231

Certificate of First Class Mailing (37 CFR 1.8(a))

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents,

Washington, D.C. 20231 on the date set forth below.

Date of Signature and of Mail Deposit

Mailin Label No. EL 833315914US

Registration No. 43,270

Attorney for Applicants

DECLARATION UNDER 37 C.F.R. 1.131 BY

GARY S. GRAY, JERRY CARSON, KASHI JAVAHERIAN, PAUL D. RENNERT AND SANDRA SILVER

Sir:

We, Gary S. Gray, Jerry Carson, Kashi Javaherian, Paul D. Rennert And Sandra Silver declare:

1. We are the inventors of the subject matter described and claimed in the above-referenced patent application.

Serial No.: 09/227,595

Prior to July 11, 1994, the invention described and claimed in the above-2. referenced application was completed in this country, as evidenced by the following:

-2-

A. Prior to July 11, 1994, we were in possession of a cloned CTLA4Ig molecule which was producing large amounts of active protein in CHO DG44 cells.

Page A-1 of Appendix A describes amino acid modifications to the Ig portion of the CTLA4Ig molecule. Deletion of the CH₂ domain from γ1 and mutations to amino acids 235 and 237 in y4 are described.

Page A-2 of Appendix A describes amplification of the mutated γ4 Hinge-CH₂-CH3 region and the cloning of the mutated γ4 into pNRDSH/hCTLA4 to replace the existing γ1 Hinge-CH₂-CH₃.

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Pages A-5 and A-6 show primers for use in making mutated forms of CTLA4Ig.

The notebook pages submitted as pages A-1 through A-7 of Appendix A demonstrate that we completed the claimed invention in this country prior to July 11, 1994.

B. In addition, as shown on page A-8 of Appendix A, prior to July 11, 1994, we demonstrated that mutated forms of CTLA4Ig effectively competed with biotinylated CTLA4-Ig for binding to B7. In the experiment presented at the bottom of the page B7Ig was put onto plates. Biotinylated CTLA4Ig was added to the plates in a fixed amount. Test forms of

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Date: _		Signed:	
			Gary S. Gray
Date:		Signed:	
			Jerry Carson
Date:	10_3_01	Signed:	Kashi Javaherian
Date:		Signed:	Paul D. Rennert
Date:		Signed:	Sandra Silver

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Gary S. Gray, Jerry Carson, Kashi Javaherian, Paul D. Rennert and Sandra Silver

Continuation of Serial No.: 09/227,595

Filed: January 8, 1999 December 20, 200

For: CTLA4-Cy4 Fusion Proteins (as amended)

Attorney Docket No.: RPN-001

Group Art Unit: 1642

Examiner: Helms, L.

Assistant Commissioner for Patents Washington, D.C. 20231

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Date of Signature and of Mail Deposit

Cabel No. EL 833315914US

Attorney for Applicants-

DECLARATION UNDER 37 C.F.R. 1.131 BY

GARY S. GRAY, JERRY CARSON, KASHI JAVAHERIAN, PAUL D. RENNERT AND SANDRA SILVER

Sir:

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We are the inventors of the subject matter described and claimed in the 1. above-referenced patent application.

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Date:	Signed:
	Gary S. Gray
Date:	Signed: Jerry Carson
Date:	Signed: Kashi Javaherian
Date: 3 October 2001	Signed: Paul D. Rennert
Date:	Signed:Sandra Silver

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Gary S. Gray, Jerry Carson, Kashi Javaherian, Paul D. Rennert and Sandra Silver

Serial No.: 09/227,595

Filed: January 8, 1999 December 20, 2001

For: CTLA4-Cy4 Fusion Proteins (as amended)

Attorney Docket No.: RPN-001

Group Art Unit: 1642

Examiner: Helms, L.

Assistant Commissioner for Patents Washington, D.C. 20231

Certificate of First Class Mailing (37 CFR 1.8(e))

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Box Paket Hylida, Washington, D.C. 20231 on the date set forth below.

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by Asylvian Megan E. Willian

Registration No. 43,270

Attorney for Applicants

DECLARATION UNDER 37 C.F.R. 1.131 BY

GARY S. GRAY, JERRY CARSON, KASHI JAVAHERIAN, PAUL D. RENNERT AND SANDRA SILVER

Sir:

We, Gary S. Gray, Jerry Carson, Kashi Javaherian, Paul D. Rennert And Sandra Silver declare:

1. We are the inventors of the subject matter described and claimed in the above-referenced patent application.

2. Prior to July 11, 1994, the invention described and claimed in the above-referenced application was completed in this country, as evidenced by the following:

A. Prior to July 11, 1994, we were in possession of a cloned CTLA4Ig molecule which was producing large amounts of active protein in CHO DG44 cells.

Page A-1 of Appendix A describes amino acid modifications to the Ig portion of the CTLA4Ig molecule. Deletion of the CH₂ domain from γ 1 and mutations to amino acids 235 and 237 in γ 4 are described.

Page A-2 of Appendix A describes amplification of the mutated $\gamma 4$ Hinge-CH₂-CH₃ region and the cloning of the mutated $\gamma 4$ into pNRDSH/hCTLA4 to replace the existing $\gamma 1$ Hinge-CH₂-CH₃.

Page A-3 of Appendix A describes a second method which involves the use of nested PCR to generate a mutated $\gamma 1$ (having an L to A substitution at amino acid 234, an L to E substitution at amino acid 235, and a G to A change at amino acid 237) from hCTLA4Ig and the cloning of the mutated $\gamma 1$ back into hCTLA4 pNRDSH.

Pages A-5 and A-6 show primers for use in making mutated forms of CTLA4Ig.

The notebook pages submitted as pages A-1 through A-7 of Appendix A demonstrate that we completed the claimed invention in this country prior to July 11, 1994.

B. In addition, as shown on page A-8 of Appendix A, prior to July 11, 1994, we demonstrated that mutated forms of CTLA4Ig effectively competed with biotinylated CTLA4-Ig for binding to B7.

In the experiment presented at the bottom of the page B7Ig was put onto plates. Biotinylated CTLA4Ig was added to the plates in a fixed amount. Test forms of CTLA4Ig were added in serial dilutions to test for their ability to compete for binding to B7 on the plate. In this type of assay as the amount of an effective competitor is increased, the amount of biotinylated CTLA4Ig that binds decreases. This leads to a decrease in the optical density readout. Unlabelled CTLA4Ig (left row) was used as a positive control.

The data show that samples #2, #3, and #4 (in rows 2, 4, and 5, respectively) effectively competed with unmodified CTLA4Ig for binding to B7. As indicated in the table in the middle of the page, sample 2 was oncoCTLA4-my4; sample 3 was IgLCTLA4-y1; and sample 4 was IgLCTLA4-y1.

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These data demonstrate that the modified CTLA4Ig molecules were still able to bind to B7.

Each of the dates deleted from pages A-1 through A-8 of Appendix A are prior to July 11, 1994.

We have been warned that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 or the United States Code, and that such willful and false statements may jeopardize the validity of the subject application or any patent resulting therefrom, and declare that all statements made of our own knowledge are true and that all statements made on information and belief are believed to be true.

Date:	Signed	: Gary S. Gray
Date:	Signed	: Jerry Carson
Date:	Signed	:Kashi Javaherian
Date: _	Signed	Paul D. Rennert
Date:	Haber 16,200/ Signed	1: Janlen Selver

Sandra Silver

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